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Survival and future need of long-term oxygen therapy for chronic obstructive pulmonary disease—gender differences

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Summary
We aimed to study trends in gender-related differences in incidence, and prevalence for long-term oxygen therapy due to chronic obstructive pulmonary disease. Another aim was to study survival after onset of oxygen therapy.
Prospectively followed were 5689 Swedish patients, who were prescribed oxygen therapy because of chronic obstructive pulmonary disease from 1987 to 2000.
The annual incidence of women starting oxygen therapy increased more rapidly than that in men. In 2000, 7.6 per 100,000 women started treatment compared with 7.1 in men. The frequency of ever smoking in Sweden in the age group receiving oxygen, i.e. age 65–84 years, was 36.4% in women and 65.0% in men, indicating that women ran a higher risk of developing an oxygen-requiring chronic hypoxaemia. An increase in women requiring oxygen therapy is predicted due to the increase in smoking frequency in young and middle-aged women and it is estimated that about 70% of Swedish patients on oxygen in 2026 will be women, with an estimated prevalence of 61 per 100,000.
In conclusion, the incidence and prevalence for long-term oxygen therapy increases more rapidly among women than in men. This is probably due to the increased frequency of smoking in women compared with men and a higher susceptibility to develop severe hypoxaemia in women. The survival is better in women with long-term oxygen therapy than in men.

Introduction

Chronic obstructive lung disease is the fifth largest cause of death worldwide.[1] Smoking is the most common cause of

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chronic obstructive pulmonary disease. In global terms, 47% of men and 12% of women smoke, corresponding to approximately one billion men and 250 million women.[2,3] The prevalence of smoking among women has increased in recent decades and today more women than men smoke in some countries, including Sweden.[4]

Long-term oxygen therapy improves survival in patients with severe hypoxaemia due to chronic obstructive pulmonary disease.[5–7] Many studies of oxygen therapy are fairly old and only a few of the patients included in them were women.[5–9] Recent studies do, however, include a larger fraction of women.[10,11]

We aimed to study trends in gender-related differences in annual incidence, and prevalence for long-term oxygen therapy due to chronic hypoxia from chronic obstructive pulmonary disease and to predict the need for oxygen therapy in the future. Another aim was to study survival after onset of oxygen therapy.

Methods

Eligible for inclusion were all the Swedish women and men aged 18 and above who received oxygen therapy from 1 January 1987 to 31 December 2000 due to severe hypoxaemia caused by chronic obstructive pulmonary disease. All the departments of respiratory medicine and all the other clinics prescribing oxygen in all 24 Swedish counties agreed on the national guidelines from the Swedish Society of Respiratory Medicine for long-term oxygen therapy, and prospectively register patients starting treatment from 1 January 1987 in a Swedish Oxygen Register.[12–14] The national guidelines for oxygen therapy were arterial oxygen tension (PaO_2) of $\leqslant$7.3 kPa for at least three weeks, including optimum medical therapy, or a PaO_2 of less than 8 kPa, with signs of right heart failure, or haematocrit of over 50%.[12,13] It was stated that oxygen should be delivered during a minimum of 16 h a day and preferably during 24 h. Excluded were patients who had been registered in centres from four of the 24 Swedish counties, since these centres withdrew from the study during some years, because of a shortage of staff. Sweden had 8.3 million inhabitants in 1987 and 8.9 million in 2000. The population in the participating counties was 7.6 million in 1987 and 8.0 million in 2000.

Arterial blood gas tensions when breathing air and oxygen, smoking history, peripheral oedema, forced expiratory volume in 1 s and forced vital capacity were registered at the start of treatment. One-year follow-up data included reasons for withdrawal. The vital status until 31 December 2003 and the dates of death were obtained from the Causes of Death Register at the Swedish National Board of Health and Welfare.

The predicted incidence and prevalence of the need for oxygen therapy were calculated from the frequency of ever smoking in Sweden in 2001 in different age groups (Table 1).[4] It was assumed that the age at the start of treatment for men and women would be the same in the future as in 2000 and that the quotient between the prevalence and incidence would be the same as from 1987 to 2000.

Every regional ethics committee in Sweden, i.e. the ethics committees in Stockholm, Göteborg, Lund, Uppsala, Umeå, Linköping and Örebro, the National Board of Health and Welfare and the Data Inspection Board approved the study. All the patients gave their informed consent.

Table 1 Prevalence of ever smoking in Sweden in 2001 according to Statistics Sweden.[4]

Age	Ever smoking (%)	
	Men	Women
16–24	23.5	30.1
25–34	33.6	37.9
35–44	43.4	52.4
45–54	63.9	59.5
55–64	69.9	54.0
65–74	64.1	41.8
75–84	66.3	30.3

Statistical analysis

Chi-squared tests were used for categorical data and *t*-tests were used for continuous data. Age-adjusted analyses of category variables were performed using logistic regression. Linear regression analyses were used for adjustments of age and other confounders in time-trend analyses of continuous variables. Time to death was analysed using Cox regression and adjusting for age. A significance level of 5% and a confidence level of 95% were used. Statistical analyses were performed with SPSS (version 11.5) and Stata (version 8.2).

Results

A total of 5689 patients were included in the final analysis, 2894 women and 2795 men. The women were 66$\pm$8 years old at the start of the study in 1987 and 73$\pm$9 years old in 2000. The men were slightly older than women: they were 67$\pm$9 years old in 1987 ($p<0.001$) and 74$\pm$8 years old in 2000 ($p<0.001$). Seventy-three percent of the women and 70% of the men had an oxygen tension (PO_2) of $\leqslant$7.3 kPa at the onset of oxygen therapy. Three hundred and ninety-four patients were excluded since they were registered in the four counties that withdrew from the study during some years. They did not differ in age and gender from the included patients.

Mean arterial PaO_2 was slightly lower and mean $PaCO_2$ was higher in women than in men when starting oxygen therapy ($p<0.001$) (Table 2). Mean $PaCO_2$ at the start of treatment gradually decreased in men from 1987 to 2000 ($p<0.001$), but it remained stable in women. The annual number of women starting oxygen therapy increased from 2.0/100,000 in 1987 to 7.6/100,000 in 2000 ($p<0.001$), while that of men rose from 2.8/100,000 in 1987 to 7.1/100,000 in 2000 ($p<0.001$) (Fig. 1). The annual incidence was higher in women than in men after 1997. The prevalence of women on oxygen increased more rapidly than that of men: 58% of the subjects using oxygen in 2000 were women (Fig. 2). The prevalence increased from 5.5/100,000 women in 1986 to 26.5/100,000 women in 2000 ($p<0.001$), while that in men rose from 5.7/100,000 to 19.3/100,000 ($p<0.001$).

Table 2 Patient characteristics at start of treatment.

	Women $n = 2894$	Men $n = 2795$	p–value
Age (years)	70±9	72±9	< 0.001
PaO_2 (kPa)	6.6±1.0	6.7±0.9	< 0.001
$PaCO_2$ (kPa)	6.6±1.2	6.1±1.2	< 0.001
PaO_2 (oxygen) (kPa)	9.0±1.1	9.0±1.2	0.95
$PaCO_2$ (oxygen) (kPa)	6.9±1.2	6.4±1.2	< 0.001
FEV_1 (litres)	0.6±0.3	1.0±0.5	< 0.001
FVC (litres)	1.4±0.5	2.1±0.9	< 0.001
Peripheral oedema (%)	58	52	<0.001
Smoking history (%)			< 0.001*
Current	4	3	
Past	85	90	
Never	11	6	

Values are presented in percent or as the means±SD. PaO_2: arterial oxygen tension; PaO_2 (oxygen): arterial oxygen tension when breathing oxygen; FEV_1: forced expiratory volume in 1 s; FVC: forced vital capacity. * The p-value refers to the whole 2×3 table.

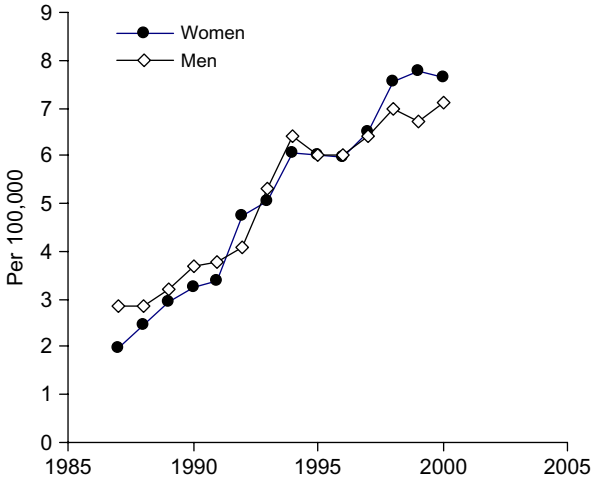

Figure 1 Annual incidence of men and women starting oxygen therapy from 1 January 1987 to 31 December 2000.

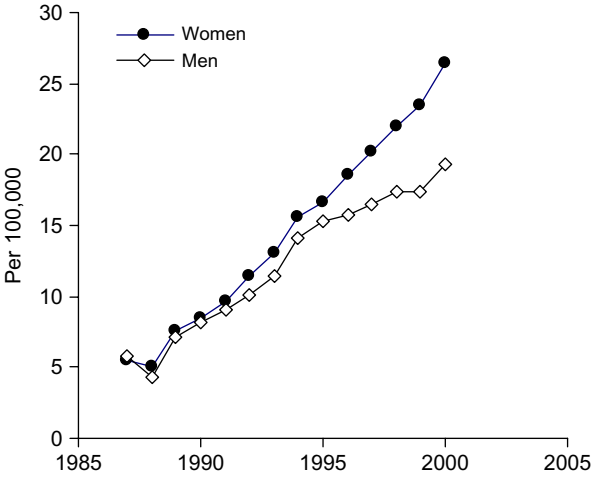

Figure 2 Annual prevalence of men and women starting oxygen therapy from 1 January 1987 to 31 December 2000.

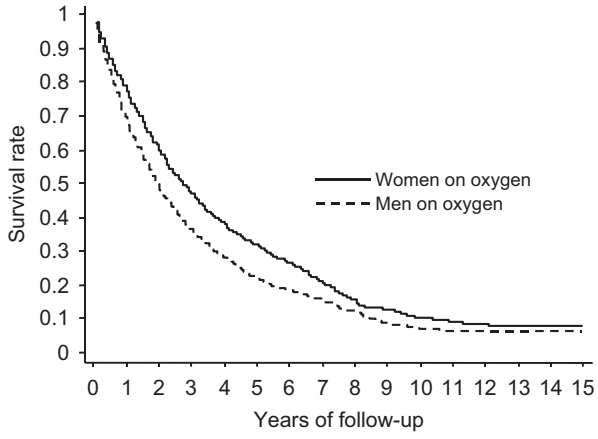

Figure 3 Survival in men and women receiving long-term oxygen therapy from 1987 to 2000.

In 1987, 42% of patients were prescribed oxygen from compressed gas cylinders and 58% were prescribed oxygen from concentrators. The percentage of patients using concentrators rose rapidly to 97% in 2000. Liquid oxygen was prescribed in 2–3% of patients after 1993, when it was introduced in Sweden. Slightly more men than women were prescribed oxygen for $\geqslant$20 h a day, $p = 0.041$. Two percent of women were prescribed oxygen for less than 15 h a day, 60% for 15–17 h a day, 9% for 18–19 h a day and 29% for 20–24 h a day. In the case of men, 2% were prescribed oxygen for less than 15 h a day, 59% for 15–17 h a day, 8% for 18–19 h a day and 31% for 20–24 h a day.

The median (first and third quartile) survival after the start of treatment was 2.8 (2.6–2.9) years in women and 2.0 (1.9–2.1) years in men (Fig. 3). First year survival was 77% (95% CI 75–79%) in women and 69% (95% CI 67–71%) in men. The relative risk of death for males vs. females was 1.21 (95% CI 1.14–1.28) according to Cox regression adjusted for age. Death was the reason for withdrawal from oxygen therapy within one year of the start of treatment in 88% of women and 91% of men. Improvement in oxygenation on

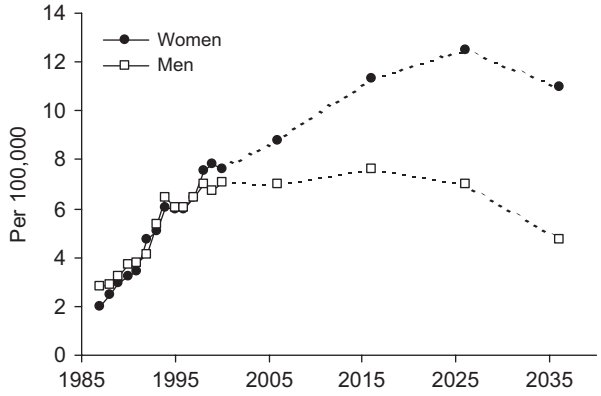

Figure 4 Predicted annual incidence of men and women starting oxygen therapy. Dashed lines indicate the predicted values.

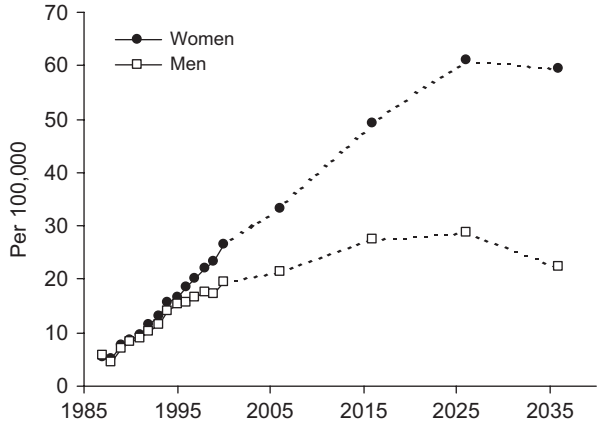

Figure 5 Predicted annual prevalence of men and women starting oxygen therapy. Dashed lines indicate the predicted values.

room air, and non-compliant patients were other reasons for withdrawal during the first year of treatment.

The frequency of ever smoking in Sweden in the age group receiving oxygen, i.e. age 65–84 years, was 36.4% in women and 65.0% in men in 2001.[4] The incidence of long-term oxygen therapy due to chronic obstructive pulmonary disease was, however, slightly higher in women in 2000, indicating that women ran a 1.9 times higher risk of developing oxygen-requiring respiratory insufficiency. The frequency of ever smoking decreased with age among women, while the opposite trend was seen in men (Table 1). The predicted incidence and prevalence of long-term oxygen therapy from 2006 to 2036 show an increase in women, due to an increase in smoking frequency among middle-aged women and a high risk of women who smoke developing end-stage chronic obstructive pulmonary disease requiring oxygen therapy. It is predicted that about 70% of patients on oxygen in 2026 will be women, with a prevalence of 61 per 100,000 women and 29 per 100,000 men. The predicted incidence of women and men requiring oxygen therapy is shown in Fig. 4 and the predicted prevalence in Fig. 5.

Discussion

The prevalence of subjects on long-term oxygen therapy increased more rapidly in women than in men during the study period due to a larger increase in women starting oxygen treatment and improved survival among women. The risk of women requiring long-term oxygen therapy was almost twice as high as that among men when smoking history was taken into consideration. Today, 58% of patients on oxygen therapy are women and this female dominance will probably increase in the near future due to many middle-aged female smokers. The survival after treatment start of oxygen therapy was significantly longer in women than in men.

There are gender differences in airway behaviour over the human life span and it has been suggested that smoking is more deleterious for lung function in women than in men.[15] The growth of lung function is slower in adolescent smoking girls than in smoking boys and women who start to smoke in childhood run a higher risk of a reduction in lung function and airway disease later in life.[16,17] Female smokers ran an increased risk for chronic obstructive pulmonary disease, and the loss of forced expiratory volume in 1 s per pack-year of smoking is also slightly higher in women.[18,19] We found no study of gender differences in susceptibility to respiratory insufficiency or the need for oxygen therapy. Since 1993, the majority of Swedish smokers have been women, but the percentage of ever-smokers was almost half as high in women than in men at the age when oxygen was started in the present study.[4,20] Women also smoked fewer cigarettes a day.[4,20] In spite of this, we found that more women than men started oxygen therapy due to chronic obstructive pulmonary disease and those women were slightly younger than men at the start of treatment. Our results indicate that the risk of respiratory failure and long-term oxygen therapy later in life is almost twice as high among female smokers compared with males, which is a new finding. Our study does not indicate that more women than men were treated because doctors are more biased to treat women. In fact, the opposite was found. The women in our study had a higher PCO_2, they were statistically more hypoxic, but probably not clinically and they more frequently had peripheral oedema than men at the start of treatment.

With few exceptions, chronic obstructive pulmonary disease in the western world is due to smoking. The fall in lung function is related to both pack-years of smoking and age.[19,21] We predicted the incidence and prevalence of oxygen therapy in the next 30 years from the frequency of ever smoking in different age groups in 2001. We suggest that the need for oxygen therapy will be stable among men but will increase in women in the near future due to an increased risk of respiratory insufficiency and an increase in smoking prevalence among young and middle-aged women.

Miyamoto et al. reported a survival of 5.2 ± 0.2 years in Japanese women and 4.8 ± 0.2 years in men after the onset of oxygen therapy.[8] They included 12,714 subjects from 1212 institutions but excluded 60% of them in their analysis. Only 25% of their patients were women. Chailleux et al. reported a median survival of 3 years among 12,043 subjects.[9] They included approximately 70% patients receiving oxygen therapy and only 16% of their patients were women. Machado et al. followed 251 men and 184 women,

and observed a median survival of about 36 months and a better survival among men.[11] Crockett et al. followed 249 men and 256 women and reported an overall first year survival of 75% and a median survival of 22 months in men and of 28 months in females.[10] A lower survival rate was observed in the present patients compared with Miyamoto et al., Chailleux et al., and Machado et al., as the median survival was only 2.8 years in women and 2.0 years in men. The survival of the present Swedish patients was, however, close to Australian patients reported by Crockett et al.[10] We included 94% of patients receiving oxygen therapy during a period of 14 years and 51% of them were women. The age, sample size and indications for oxygen therapy were about the same in all studies. Differences in patient selection could still explain some of the differences in survival rate. However, 63% of patients in the study by Miyamoto et al. used oxygen for at least 20 h a day,[8] while only 30% were prescribed to use it for 20 h or more in the present study. The "NOTT" study from 1980 found an increase in survival in subjects who were told to use oxygen therapy continuously for 24 h compared with those who were told to use it for 12 h a day.[6] The low survival in Sweden for both women and men on oxygen therapy could therefore be due to the prescription to use it for about 16 h a day in the majority of cases and not for 20–24 h a day.

One limitation of the present study is that we predict the need for long-term oxygen therapy in relation to ever smoking, and that we do not take into account a possible effect of increased smoking cessation which could lower the estimated need for oxygen therapy in the future. We also forecast the need for oxygen therapy during the next 35 years from only 15 years of observation and the absolute values are probably not reliable at the end of the prediction period.

The present study was undertaken in the best possible circumstances. Sweden is a fairly small, well-organised country and the economic situation for most inhabitants, including women, is good. The health care system is organised in counties and all the hospitals and primary care centres are either owned or supported by the county council. The medical service, including equipment for long-term oxygen therapy, was free and no changes in management guidelines or reimbursement for long-term oxygen therapy occurred after 1986. Only doctors specialising in respiratory medicine prescribed oxygen and it was impossible to purchase oxygen equipment outside the medical care system during the study period. Sweden has very good official statistics relating to medical diagnoses, treatments and causes of deaths. American and European guidelines for starting long-term oxygen therapy are still the same as in the present study.[22] All centres and all doctors prescribing oxygen took part in the present prospective study, with the exception of centres in four counties in certain years because of a shortage of staff. Around 9% of the population lived in these four counties and excluded patients did not differ in age and gender from included patients. The exclusion is regarded as being of minor relevance without any chance of affecting the present results.

Patients starting oxygen therapy in Sweden today differ from patients constituting the evidence of treatment and in previous large follow-up studies of mortality.[5,6,8,9] In the majority of cases, they are women. The number of disabled women requiring continuous oxygen therapy will increase still further, not only in Sweden but probably also in global terms, as smoking has increased among women and the tobacco industry is marketing cigarettes to young women in most countries.[23,24]

In conclusion, the incidence and prevalence for long-term oxygen therapy increase more rapidly among women than in men. This is probably due to the increased frequency of smoking in women compared with men and a higher susceptibility to develop severe hypoxaemia in women. The survival during long-term treatment of oxygen therapy is better in women than in men. There is an obvious risk of a large increase in a near future in the number of women requiring oxygen therapy.

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